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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,554	01/14/2004	Christine Lindsay Mummery	17360	5975

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EXAMINER	
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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,554	MUMMERY, CHRISTINE LINDSAY	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *9,45,46,50-54,60,61,63-65,68-71 and 87-89* is/are pending in the application.

4a) Of the above claim(s) *63 and 91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,46,50-54,60,61,64,65,68-71 and 87-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 10/26/2009have been fully considered. Claims 45-46, 50-54, 60-61, 63-65, 68-71, 87-89, 91 are pending. Claims 63, 91 are withdrawn to a non-elected invention. Claims 1-44, 47-49, 55-59, 62, 66-67, 72-86, 90, 92-132 are canceled.

Claims 45-46, 50-54, 60-61, 64-65, 68-71, 87-89 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 51 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 51, the phrase "visceral endoderm-like" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 60, the phrase "substantially" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be

patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 45-46, 50-54, 60, 64-65, 68-71, 87-89 under 35 U.S.C. 103(a) as being unpatentable over **Reubinoff et al** (Nature Biotechnology, 18: 399-404, 2000) in view of **van den Eijnden-van Raaij et al,** (Mechanisms of Development, 33: 157-166, 1991 (IDS)); **Skerjanc,** (Trends Cardiovasc Med 1999;9:139–143, 1999); **Itskovitz-Eldor et al**, (WO 00/70021) is withdrawn.

Claims 45-46, 50-54, 60, 64-65, 68-71, 87-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Amit et al** (Developmental Biology, 227: 271-278, 2000) in view of **Mummery et al** (Differentiation, 46: 51-60, 1991); **Rohwedel et al** (Cells Tissues Organs, 165:190-202, 1999 (Abstract)); **Rohwedel et al** (Dev Biol, 164(1): 87-101, 1994 (IDS)).

Amit et al teach co culture of human embryonic stem cells (hES) plated on irradiated mouse embryonic fibroblasts (MEFs) (p 272, under materials and methods). Amit teaches the fibroblast feeder layer remains the most poorly defined component of the human ES cell culture environment (p 276, 2nd column last paragraph bridge to p 277). Unlike undifferentiated mouse ES cells, which can be cultured using leukemia inhibitory factor (LIF) in the absence of fibroblasts under current culture conditions, addition of LIF to the medium does not allow the culture of human ES cells in the absence of feeder layers. If LIF and bFGF are added in combination, human ES cells are still lost to differentiation in the absence of fibroblasts p 277). To date we have also been unable to demonstrate beneficial effects of exogenously added LIF in the presence of fibroblasts (p 277). Amit suggests however, fibroblasts can produce LIF, and given the importance of LIF in the culture of human embryonic germ (EG) cells further examination of the role of LIF in human ES cell self-renewal is warranted. Identifying the factors

that the fibroblasts produce that promote human ES cell renewal will be critical to the large-scale growth of ES cells, because the feeder layers are labor intensive to prepare and because variation between batches of fibroblasts can introduce undesirable variation and complexity to experiments (p277). Amit teaches that serum is a complex mixture that can contain compounds both beneficial and detrimental to human ES cell culture (p 276, 1st column). Different serum batches vary widely in their ability to support vigorous undifferentiated proliferation of human ES cells (p 276). Replacing serum with defined components should reduce the variability of experiments associated with serum batch variation and should allow more carefully defined differentiation studies (p 276). Amit suggests the need for substantial improvements to the serum-free culture of human ES cells (p 276) as well as the fibroblast feeder layer remains the most poorly defined component of the human ES cell culture environment. Amit suggests most important, the present culture conditions support a cloning efficiency of human ES cells (<1%) that is considerably lower than the cloning efficiency of mouse ES cells in order to apply signaling to mouse ES cells technology, such as homologous recombination, will be very difficult to apply to human ES cells (p 276). Amit differs from the present invention for not teaching the co-culture of END-2 cells with human embryonic stem cells (hES).

However, at the time of the instant invention **Mummery et al** teaches co culture of PI9 embryonal carcinoma (EC) cells with the feeder END-2 cells. Mummery teaches that when PI9 embryonal carcinoma (EC) cells were co cultured with cells from one of several established visceral-endoderm-like cell lines, the EC cells were rapidly induced to aggregate and differentiate, into cell types including mesoderm-derived cardiac and skeletal muscle. Mummery suggests that aggregation was necessary, but not sufficient to make P19 EC cells differentiate. Direct contact between the two cell types was not necessary, since even when separated by an agar layer in co cultures, aggregates of PI9 still differentiated. Mummery suggests that medium

conditioned by cells of the END-2 line, a visceral-endoderm-like derivative of PI 9, was particularly potent in inducing endodermal and mesodermal differentiation of single PI9 aggregates, confirming the involvement of a diffusible factor secreted specifically by visceral-endoderm-like cells in this process (abstract). Mummery also teaches that the addition of 10^{-9}M retinoic acid into the charcoal stripped-FCS supplemented medium the cells became sensitive to the inducing action of RA, forming beating muscle at 10^{-9}M retinoic acid (p 58, 1st column last paragraph). **Rohwedel et al (1999)** teach induction of cellular differentiation by retinoic acid in vitro (title). Rohwedel et al teach cellular differentiation by retinoic acid (RA) has been studied with undifferentiated pluripotent embryonic carcinoma (EC) and embryonic stem (ES) cells in vitro. Both cellular systems are suitable to study differentiation of various cell types, because they recapitulate early stages of mouse embryogenesis (abstract). Rohwedel et al teach in vivo, RA was identified as a morphogenic and teratogenic compound and furthermore as a signaling molecule influencing gene expression in a complex manner via a family of RA receptors. Rohwedel et al teach in vitro studies with ES and EC cells in comparison to in vivo studies that have contributed to our understanding how RA influences differentiation and regulates gene expression (abstract). Rohwedel et al teach that modulation of ES cell differentiation in vitro by RA depends on the concentration and developmental stage of application which is comparable to its stage-dependent influence on embryonic development in vivo (abstract). **Rohwedel et al (1994)** teach the mouse blastocyst-derived embryonic stem cell (ES cell) line BLC6 efficiently differentiates into myosin heavy chain-, desmin- and myogenin-positive skeletal muscle cells when cultivated in embryo-like aggregates (embryoid bodies). Rohwedel teaches during myocyte differentiation the density of L-type Ca2+ channels significantly increases while the density of T-type Ca2+ channels decreases. The effect of external signals on myogenic differentiation of BLC6 cells was demonstrated by cocultivation with visceral endodermal END-2

cells and the activin A-secreting WEHI-3 cells. Rohwedel suggests the early steps of muscle development in vivo and may serve as an excellent in vitro system to study this process (abstract).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of co culture system of Amit to utilizing EDN-2 cells instead of MEFs to co culture hES cells, such as that taught by Mummery, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to make this modification in order to induce cellular differentiation of hES cells by retinoic acid (RA) as has been suggested by Rohwedel et

al (1999) where undifferentiated pluripotent embryonic carcinoma (EC) and embryonic stem (ES) cells in vitro and where both cellular systems are suitable to study differentiation of various cell types, because they recapitulate early stages of mouse embryogenesis and moreover by the teachings of Amit where . This is further underscored by the teachings of Rohwedel et al (1994) who teach the mouse blastocyst-derived embryonic stem cell (ES cell) efficiently differentiates into myosin heavy chain-, desmin- and myogenin-positive skeletal muscle cells when cultivated in EBs during myocyte differentiation the density of L-type Ca2+ channels significantly increases while the density of T-type Ca2+ channels decreases and the effect of external signals on myogenic differentiation is induced by cocultivation with visceral endodermal END-2 cells and the activin A-secreting WEHI-3 cells which suggests the early steps of muscle development in vivo and may serve as an excellent in vitro system to study myogenic differentiation (abstract).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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